Chromosome Number Diseases

Introduction

This lesson is about disorders of chromosome number. Not genes or alleles, but **entire chromosomes.** Alteration in the chromosome set isn't well tolerated. Most disorders of this nature are nonviable.

There are two types of chromosome disorder:

Euploid disorders are fatal; they're often caused by multiple fertilization or entire failure of a cell to divide. The entire chromosome set is copied. There will be multiples of 23 chromosomes.

Aneuploid disorders are often caused by nondisjunction (95%) or Robertsonian translocation (5%). Recurrence risk is discussed in lesson #2 and in the next lesson.

Euploidy

Euploidy means that there is **any multiple of 23 chromosomes.** That doesn't mean genetic material, chromatids, alleles, or genes. That is **chromosomes**. Because any alteration in the complement of chromosomes that maintains euploidy means that **every chromosome is duplicated**, there must be some severe event that can't be attributed to nondisjunction.

A **gamete** is a **haploid** cell and so has **1n, 23 chromosomes**, or **one-half** of a somatic cell. A **somatic** cell is **diploid**, has **2n**, or **46 chromosomes**, or the normal number of most of our cells. **Triploid cells** (3n or 69 chromosomes) can be **brought to term** but are **always fatal**. Triploid pregnancies more often result in molar complications than in a normal fetus. Triploid pregnancies result from **two sperm fertilizing one egg**. Tetraploid cells (4n or 92 chromosomes) are terrifically difficult to achieve and **never reach term.**

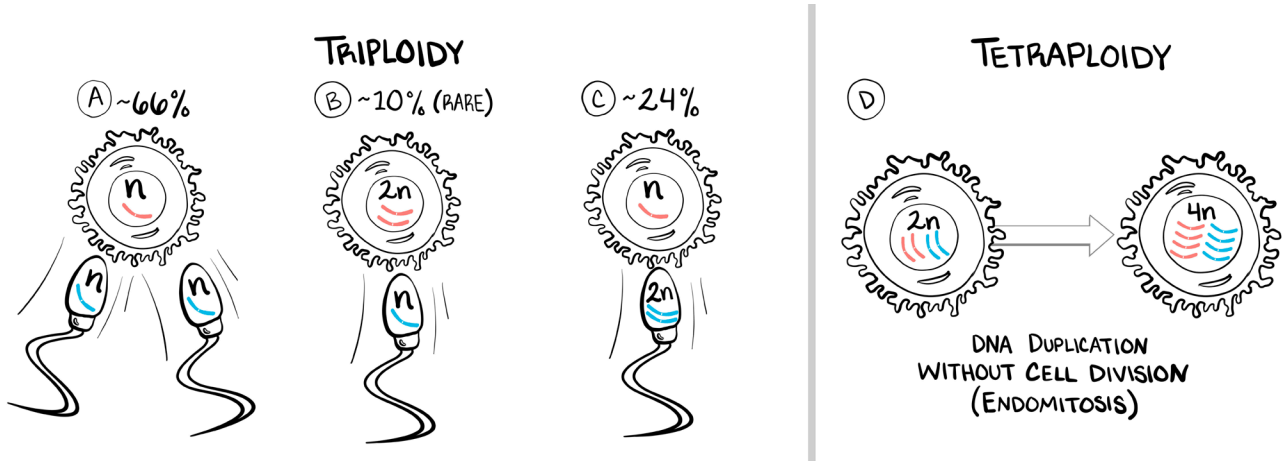

Figure 6.1: Triploidy and Tetraploidy Mechanisms
Triploidy's mechanism should be learned as (A) two normal sperm fertilizing a normal egg. Though it's possible that (B) the egg has a full complement of chromosomes, or (C) the sperm has a full complement, those mechanisms suggest total failure of meiosis II, and no cell division, which is much rarer than dispermy. Tetraploidy's (D) mechanism is endomitosis—duplication of a fertilized egg's chromosomes but total failure of mitosis.

Euploid does not mean "a normal number" of chromosomes. It means only that the **entire chromosome set was duplicated**.

Aneuploidy

Aneuploidy is **any number of chromosomes** that is **not a multiple of 23**.

A human zygote can tolerate only **a single chromosome change**—which means that all aneuploid patients will have either 45 (missing one) or 47 (one too many) chromosomes.

Any **somatic monosomy** dies. So in the **45-chromosome patients who live**, their deficiency must be of the **sex chromosome**.

The only **viable somatic trisomies** (extra copy) are of Down syndrome (trisomy 21), Edwards (trisomy 18), and Patau (trisomy 13). The **viable sex-chromosome** disorders are Klinefelter (47,XXY) and Turner (45,XO).

Aneuploidy can be caused by translocations but are far more common in **nondisjunction**.

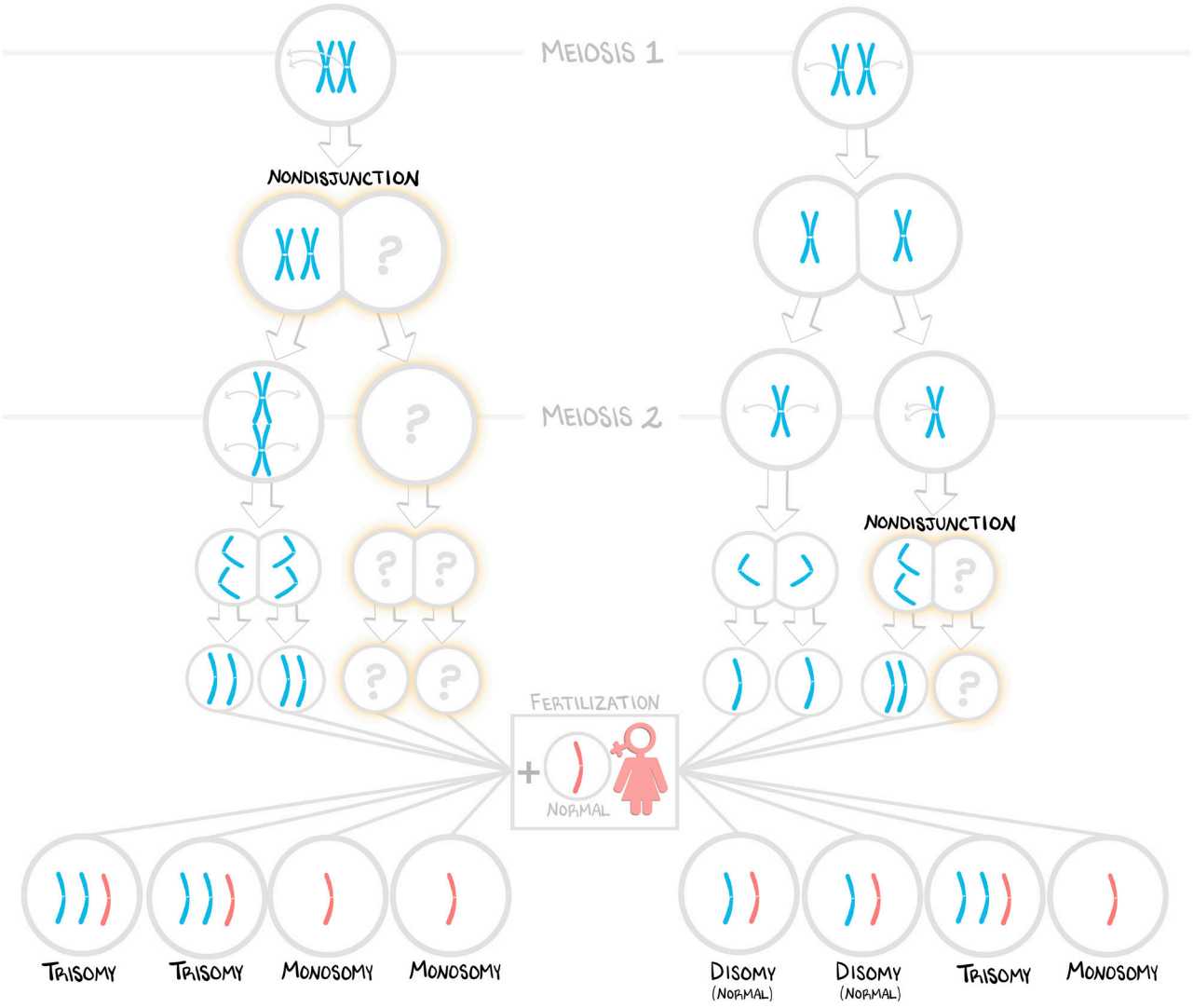

Figure 6.2: Nondisjunction Causes Monosomy and Trisomy
Regardless of whether nondisjunction occurs in meiosis I or meiosis II, potentially abnormal gametes are made. Nondisjunction in meiosis I ensures that all gametes have abnormal complements of chromosomes. Nondisjunction in meiosis II provides opportunity for normal gametes. When the abnormal gametes (blue) fertilize with a normal gamete (yellow) the result can be trisomy (three copies), monosomy (one copy), or disomy (normal, and only in the case of nondisjunction of meiosis II). Anything in the "progeny possibilities" row that's not "2" is abnormal.

If **sister homologous chromosomes** fail to separate in **meiosis I** or **sister chromatids** fail to separate in **meiosis II**, the resulting gamete has either one extra (will result in trisomy) or one too few (will result in monosomy) of the one chromosome. **Nondisjunction, the failure of chromosomes to separate**, can't predict which of the gametes will be fertilized—each of the four outcomes of both nondisjunction examples can live. However, if the gamete that fertilizes has **one fewer chromosome** than normal, the combination of a normal egg with the missing-chromosome-gamete results in a **monosomy** for that one chromosome. If that gamete that fertilizes has **one extra chromosome**, the combination of the normal egg with the extra-set-gamete will result in a **trisomy** for that one chromosome.

Down Syndrome

Down syndrome is **trisomy 21** and is caused by **nondisjunction** (95%) or **Robertsonian translocation** (5%, discussed in the next lesson). 21 is the drinking age in the United States, and Down starts with a D, just as drinking does, a mnemonic that it's trisomy 21. Trisomy 21 is the **most common genetic disorder of chromosome number** (because it's the only one that can survive). Patients affected have **intellectual disability** of varying severity—some are independent, some are institutionalized. There's also a characteristic **syndromic face** with upward slanted eyes, small head and ears, and flat facial features. A **single palmar crease** is found on the hands. **Ventral septal defects**, a product of **endocardial cushion defects**, are common and can be assessed with an echocardiogram. Because the APP gene which produces a protein associated with Alzheimer's is on chromosome 21, and an extra chromosome means extra expression of that gene, Down syndrome patients often develop **early Alzheimer's** on top of their intellectual disability (in their 40s). Other associated disorders are Hirschsprung's and duodenal atresia (GI topic). Screening is available for Down syndrome. There are several options available throughout pregnancy. Screening tools should only be used if the mother is willing to **accept increased risk for confirmatory testing** and **desires abortion if positive**. If not, there's nothing that can be done, and the risk to the pregnancy is logical only if there's an action to be taken.

A **first-trimester screen** involves a maternal blood test and an ultrasound assessing for **nuchal translucency**.

A **second-trimester screen** is more popular, named the **quad-screen**. In the quad-screen in a Down syndrome patient, the **AFP** and **estriol are decreased**, while the β-**hCG** and **inhibin A** are **increased.** Down syndrome follows the "contra code"—down down, up up.

Edwards Syndrome

Edwards syndrome begins with an E, as does the word election. The voting (election) age in the United States is 18. This is the way to remember that **Edwards is Trisomy 18**. Edwards syndrome pregnancies are brought to term, but the babies will **always die within one year** and usually **die within one month**. The syndrome reveals **clenched fists** with **overlapping fingers** and **rocker-bottom feet**. Edwards and Patau patients share congenital heart defects, neural-tube defects, and small facial features. There is no treatment.

An Edwards syndrome quad-screen shows a normal AFP, very low hCG, low estriol, and normal inhibin A.

Patau Syndrome

Patau syndrome starts with a P, just like a PG-13 movie, reminding you that it's **trisomy 13**. These patients are born but will **never live one month**, and **usually die day one**. They have **extra digits**, **cleft lip/palate**, and shared features with Edwards. There's no treatment.

A Patau syndrome quad-screen shows an increased AFP and normal remainder. "*AFPatau.*"

Klinefelter Syndrome (47,XXY)

Diagnosis of Klinefelter syndrome is made by seeing a **Barr body in a male**. Barr bodies are found in cells with two X chromosomes one of which undergoes inactivation. In any normal chromosome set, two X chromosomes negates the possibility of a Y chromosome. But in Klinefelter there could be a genotypically male individual (having a Y chromosome comes with genes to switch the default female to male) with an inactivated extra X chromosome. The syndrome is characterized by **testicular atrophy**. Because of this, the pituitary increases the secretion of FSH and LH, which activates non-testicular hormone production of **estrogen** resulting in a **high-pitched voice**, **gynecomastia**, and **female body-hair distribution**. They're often tall, lanky, and have an intellectual disability.

Turner Syndrome (45;XO)

Diagnosis of Turner syndrome is made by **failing to see a Barr body in a female**. Barr bodies are found when a cell has two X chromosomes and one inactivates. If there's no Barr body and an X chromosome, then there must be a missing X chromosome. While Turner syndrome can still present with a 46,XX set, it would be unfair to do this on an exam. The main foundation of the syndrome is **streak ovaries**. Incapable of producing estrogen or progesterone, the patient experiences no growth spurt during puberty (and so has a **short stature**) and also experiences **primary amenorrhea**. When given exogenous hormones, **she can have menstrual cycles**. The characteristics of the syndrome include **broad shield-like chest** with **wide-spaced nipples**, a **webbed neck,** and there is an association with **coarctation of the aorta**. Get an echocardiogram to assess.

Disease	Organizer	Genetics	Details
Down	Drinking age	Tri 21	Most common chromosome disorder, intellectual disability Flattened face, small ears, slanting eyes, single palmar crease VSD, Hirschsprung's, duodenal atresia, early Alzheimer's (APP gene on chromosome 21) Quad screen: ↑β-hCG, ↑inhibin A, ↓AFP, ↓estriol
Edwards	Election (voting) age	Tri 18	Never lives 1 year, most die 1 month Clenched fists with overlapping fingers, rocker-bottom feet Congenital heart, neural tube defects, small face, head, jaw
Patau	PG-13 age	Tri 13	Never lives 1 month, most die on day 1 Extra digits, cleft lip / palate Congenital heart, neural-tube defects, small head
Klinefelter	Male	47,XXY	Male with Barr body Testicular atrophy, gynecomastia, female body-hair distribution, high-pitched voice, intellectual disability
Turner	Female	45,X0	Female without Barr body Broad, shield-like chest, webbed neck, primary amenorrhea, short stature because of failed ovarian hormones Ultrasound shows streak ovaries ↑FSH, ↑LH, but ↓progesterone and ↓estrogen (no ovaries) Coarctation of the aorta—get an echo

Table 6.1: Disorders of Chromosome Number, Summary